



## General

### Guideline Title

Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline.

### Bibliographic Source(s)

Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, Curren K, Balter MS, Bhutani M, Camp PG, Celli BR, Dechman G, Dransfield MT, Fiel SB, Foreman MG, Hanania NA, Ireland BK, Marchetti N, Marciniuk DD, Mularski RA, Ornelas J, Road JD, Stickland MK. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015 Apr;147(4):894-942. [285 references] [PubMed](#)

### Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Recommendations

### Major Recommendations

The grades of recommendation (1A–2C, consensus based) and the approach to rating the quality of evidence are defined at the end of the "Major Recommendations" field.

Population, Intervention, Comparator, and Outcome (PICO) 1: Do Nonpharmacologic Treatments and Vaccinations Prevent/Decrease Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD)?

1. In patients with COPD, the panel suggests administering the 23-valent pneumococcal vaccine as part of overall medical management but did not find sufficient evidence that pneumococcal vaccination prevents acute exacerbations of COPD (Grade 2C).
2. In patients with COPD, the panel recommends administering the influenza vaccine annually to prevent acute exacerbations of COPD (Grade 1B).
3. In patients with COPD, the panel suggests including smoking cessation counseling and treatment using best practices as a component of a comprehensive clinical strategy to prevent acute exacerbations of COPD (Grade 2C).
4. In patients with moderate, severe, or very severe COPD who have had a recent exacerbation (i.e.,  $\leq 4$  weeks), the panel recommends pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 1C).
5. In patients with moderate, severe, or very severe COPD who have had an exacerbation greater than the past 4 weeks, the panel does not suggest pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 2B).
6. In patients with COPD, the panel suggests that education alone should not be used for prevention of acute exacerbations of COPD.

(Ungraded Consensus-Based Statement).

7. In patients with COPD, the panel suggests that case management alone should not be used for prevention of acute exacerbations of COPD (Ungraded Consensus-Based Statement).
8. In patients with COPD with a previous or recent history of exacerbations, the panel recommends education and case management that includes direct access to a health-care specialist at least monthly to prevent severe acute exacerbations of COPD, as assessed by decreases in hospitalizations (Grade 1C).
9. In patients with moderate to severe COPD, the panel suggests education together with an action plan but without case management does not prevent severe acute exacerbations of COPD, as assessed by a decrease in emergency department (ED) visits or hospitalizations over a 12-month period (Grade 2C).
10. For patients with COPD, the panel suggests education with a written action plan and case management for the prevention of severe acute exacerbations of COPD, as assessed by a decrease in hospitalizations and ED visits (Grade 2B).
11. For patients with COPD, the panel suggests that telemonitoring compared with usual care does not prevent acute exacerbations of COPD, as assessed by decreases in emergency room visits, exacerbations, or hospitalizations over a 12-month period (Grade 2C).

#### PICO 2: Does Maintenance Inhaled Therapy Prevent/Decrease Acute Exacerbations of COPD?

12. In patients with moderate to severe COPD, the panel recommends the use of long-acting  $\beta_2$ -agonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1B).
13. In patients with moderate to severe COPD, the panel recommends the use of a long-acting muscarinic antagonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1A).
14. In patients with moderate to severe COPD, the panel recommends the use of long-acting muscarinic antagonists compared with long-acting  $\beta_2$ -agonist to prevent moderate to severe acute exacerbations of COPD (Grade 1C).
15. In patients with moderate to severe COPD, the panel suggests the use of a short-acting muscarinic antagonist compared with short-acting  $\beta_2$ -agonist monotherapy to prevent acute mild-moderate exacerbations of COPD (Grade 2C).
16. In patients with moderate to severe COPD, the panel suggests the use of short-acting muscarinic antagonist plus short-acting  $\beta_2$ -agonist compared with short-acting  $\beta_2$ -agonist alone to prevent acute moderate exacerbations of COPD (Grade 2B).
17. In patients with moderate to severe COPD, the panel suggests the use of long-acting  $\beta_2$ -agonist monotherapy compared with short-acting muscarinic antagonist monotherapy to prevent acute exacerbations of COPD (Grade 2C).
18. In patients with moderate to severe COPD, the panel recommends the use of a long-acting muscarinic antagonist compared with a short-acting muscarinic antagonist to prevent acute moderate to severe exacerbations of COPD (Grade 1A).
19. In patients with moderate to severe COPD, the panel suggests the combination use of a short-acting muscarinic antagonist plus long-acting  $\beta_2$ -agonist compared with long-acting  $\beta_2$ -agonist monotherapy to prevent acute mild to moderate exacerbations of COPD (Grade 2C).
20. For patients with stable moderate, severe, and very severe COPD, the panel recommends maintenance combination inhaled corticosteroid/long-acting  $\beta_2$ -agonist therapy (and not inhaled corticosteroid monotherapy) compared with placebo to prevent acute exacerbations of COPD (Grade 1B).
21. For patients with stable moderate, severe, and very severe COPD, the panel recommends maintenance combination inhaled corticosteroid/long-acting  $\beta_2$ -agonist therapy compared with long-acting  $\beta_2$ -agonist monotherapy to prevent acute exacerbations of COPD (Grade 1C).
22. For patients with stable moderate to very severe COPD, the panel recommends maintenance combination inhaled corticosteroid/long-acting  $\beta_2$ -agonist therapy compared with inhaled corticosteroid monotherapy to prevent acute exacerbations of COPD (Grade 1B).
23. For patients with stable COPD, the panel recommends inhaled long-acting anticholinergic/long-acting  $\beta_2$ -agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).
24. For patients with stable COPD, the panel recommends maintenance combination of inhaled corticosteroid/long-acting  $\beta_2$ -agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).
25. For patients with stable COPD, the panel suggests maintenance combination of inhaled long-acting anticholinergic/corticosteroid/long-acting  $\beta_2$ -agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 2C).

#### PICO 3: In Patients Aged. 40 Years Who Are Previous or Current Smokers With COPD, Does Oral Therapy Prevent/Decrease Acute Exacerbations of COPD?

26. For patients with moderate to severe COPD, who have a history of one or more moderate or severe COPD exacerbations in the previous year despite optimal maintenance inhaler therapy, the panel suggests the use of a long-term macrolide to prevent acute exacerbations of

COPD (Grade 2A).

27. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, the panel suggests that systemic corticosteroids be given orally or intravenously to prevent hospitalization for subsequent acute exacerbations of COPD in the first 30 days following the initial exacerbation (Grade 2B).
28. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, the panel recommends that systemic corticosteroids not be given orally or intravenously for the sole purpose of preventing hospitalization due to subsequent acute exacerbations of COPD beyond the first 30 days following the initial acute exacerbation of COPD (Grade 1A).  
*Remark:* This does not preclude the use of systemic corticosteroids for the treatment of acute exacerbations of COPD.
29. For patients with moderate to severe COPD with chronic bronchitis and a history of at least one exacerbation in the previous year, the panel suggests the use of roflumilast to prevent acute exacerbations of COPD (Grade 2A).
30. For stable patients with COPD, the panel suggests treatment with oral slow-release theophylline twice daily to prevent acute exacerbations of COPD (Grade 2B).
31. For patients with moderate to severe COPD and a history of two or more exacerbations in the previous 2 years, the panel suggests treatment with oral N-acetylcysteine to prevent acute exacerbations of COPD (Grade 2B).
32. For stable outpatients with COPD who continue to experience acute exacerbations of COPD despite maximal therapy designed to reduce acute exacerbations of COPD, the panel suggests that oral carbocysteine could be used to prevent acute exacerbations where this therapy is available (Ungraded Consensus-Based Statement).
33. For patients with moderate to severe COPD who are at risk for COPD exacerbations, the panel does not recommend using statins to prevent acute exacerbations of COPD (Grade 1B).

#### Definitions:

#### Rating the Confidence in the Estimate of the Effect

Quality of the Evidence	Level of Confidence in the Estimate of the Effect
High	Very confident that the true effect lies close to that of the estimate of the effect
Moderate	Moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

#### American College of Chest Physicians Grading System

Grade of Recommendation	Balance of Benefit vs. Risk and Burdens	Methodological Strength of Supporting Evidence	Implications
Graded evidence-based guideline recommendations			
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Strong	Benefits clearly outweigh	Evidence for at least one critical	Recommendation can apply to most patients in

recommendation, Grade of Recommendation low- or very-low-quality evidence (1C)	risk and burdens or vice versa Balance of Benefit vs. Risk and Burdens	outcome from observational studies, case series, or from RCTs with serious methodological flaws or indirect evidence Methodological Strength of Supporting Evidence	many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate. Implications
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient's or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patient's or societal values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Nongraded consensus-based suggestions			
Consensus-based (CB)	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on confidence in the estimate of effect and may change the estimate.

## Clinical Algorithm(s)

None provided

## Scope

## Disease/Condition(s)

Chronic obstructive pulmonary disease (COPD)

## Guideline Category

Prevention

Treatment

## Clinical Specialty

Pulmonary Medicine

## Intended Users

Advanced Practice Nurses

Nurses

Pharmacists

Physician Assistants

Physicians

## Guideline Objective(s)

To provide a practical, clinically useful document to describe the current state of knowledge regarding the prevention of acute exacerbations of chronic obstructive pulmonary disease (COPD) according to major categories of prevention therapies

## Target Population

Patients with chronic obstructive pulmonary disease (COPD)

## Interventions and Practices Considered

### Prevention/Treatment

1. Pneumococcal vaccine
2. Influenza vaccine annually
3. Smoking cessation counseling and treatment
4. Pulmonary rehabilitation (patients with moderate, severe, or very severe chronic obstructive pulmonary disease [COPD] who have had a recent exacerbation [i.e., 4 weeks])
5. Patient education
  - With case management that includes direct access to a health-care specialist at least monthly
  - With a written action plan and case management
6. Long- or short-acting  $\beta_2$ -agonists
7. Long- or short-acting muscarinic antagonists
8. Short-acting muscarinic antagonist plus short-acting  $\beta_2$ -agonist
9. Combination inhaled corticosteroid/long-acting  $\beta_2$ -agonist therapy
10. Combination inhaled long-acting anticholinergic/long-acting  $\beta_2$ -agonist therapy
11. Inhaled long-acting anticholinergic monotherapy
12. Macrolide
13. Systemic corticosteroids (to prevent hospitalization for subsequent acute exacerbations of COPD in the first 30 days following the initial exacerbation)
14. Roflumilast
15. Oral slow-release theophylline
16. Oral N-acetylcysteine
17. Oral carbocysteine

Note: The following interventions were considered but not recommended:

- Pulmonary rehabilitation for patients with moderate, severe, or very severe COPD who have had an exacerbation greater than the past 4 weeks
- Patient education alone
- Case management alone
- Patient education together with an action plan but without case management
- Telemonitoring compared with usual care for prevention of acute exacerbations
- Systemic corticosteroids for the sole purpose of preventing hospitalization due to subsequent acute exacerbations of COPD beyond the first

30 days following the initial acute exacerbation of COPD

- Statins

## Major Outcomes Considered

- Worsening lung function
- Quality of life
- Urgent care or hospitalization
- Cost of care

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

#### Literature Searches

All panelists reviewed the population, intervention, comparator, and outcome (PICO) questions and finalized the search terms, inclusion and exclusion criteria, and databases that would be searched (see Table 2 in the original guideline document). The Guidelines International Network (GIN) Library and the National Guideline Clearinghouse (NGC) were used to search for guidelines on chronic obstructive pulmonary disease (COPD), and PubMed and the Cochrane Library were used to search for systematic reviews and primary literature.

The searches for guidelines were conducted on January 30, 2013, and included all guidelines published up to that date. The GIN search netted 26 guidelines, whereas the NGC search netted 24; only six of these were not found in the GIN search. In total, eight guidelines were considered relevant and were assessed for quality using the AGREE (Appraisal of Guidelines Research & Evaluation) II instrument. 25 Guidelines were excluded if they did not cover one of the three interventions (nonpharmacologic therapies, inhaled therapies, and oral therapies), did not cover the outcome of interest (prevention of acute exacerbations of COPD), or were not an evidence-based guideline.

The Cochrane search for systematic reviews took place on April 25, 2013, and was limited to systematic reviews published between 2007 and 2013. The PubMed search was conducted on April 29, 2013, and was limited to reviews published between 2008 and 2013. The search of the Cochrane Library resulted in 127 systematic reviews, and an additional 14 systematic reviews were found in the PubMed search. The systematic reviews were categorized by topic and sent to the three PICO groups for study selection. Relevant systematic reviews were assessed for quality using the DART (Documentation and Appraisal Review Tool) to further determine whether they would be used to directly inform the evidence base for recommendations. Any fair- or good-quality systematic reviews used in this manner were updated through the search strategies used by the review authors. Systematic reviews were also scanned for references that could further inform the primary literature searches.

#### Literature Searches by PICO Group

The PICO 1 nonpharmacologic therapies group reviewed 49 systematic reviews and determined that 15 were relevant. Of the 15 systematic reviews, four were used to directly inform the evidence base. The PICO 1 group conducted primary literature searches and reviews for the questions on education, action plans, case management, and smoking cessation because existing systematic reviews did not meet the predefined definitions for these interventions. The PICO 2 inhaled therapies group reviewed 49 systematic reviews and determined that 30 were relevant. Of the 30 systematic reviews, 11 were used to directly inform the evidence base. The PICO 3 oral therapies group reviewed 27 systematic reviews and determined that eight were potentially relevant. The PICO 3 group also conducted primary literature reviews because the extracted systematic reviews did not sufficiently address all the drug classes. Additional details on literature searches and study selection can be found in e-Appendix 1 in the supporting data (see the "Availability of Companion Documents" field).

## Number of Source Documents

- The population, intervention, comparator, and outcome (PICO) 1 nonpharmacologic therapies group: four systematic reviews were used to directly inform the evidence base.
- The PICO 2 inhaled therapies group: 11 systematic reviews were used to directly inform the evidence base.
- The PICO 3 oral therapies group: eight systematic reviews were potentially relevant.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

### Rating Scheme for the Strength of the Evidence

Rating the Confidence in the Estimate of the Effect

Quality of the Evidence	Level of Confidence in the Estimate of the Effect
High	Very confident that the true effect lies close to that of the estimate of the effect
Moderate	Moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

## Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

### Study Selection and Data Extraction

A methodologist assigned to each population, intervention, comparator, and outcome (PICO) group conducted the initial literature searches and the first-round title and abstract review to exclude studies not related to chronic obstructive pulmonary disease (COPD) based on the inclusion and exclusion criteria shown in Table 2 in the original guideline document. The panelists reviewed the studies identified for exclusion and divided into pairs to apply the inclusion and exclusion criteria to the studies initially screened for inclusion. All recommendations were made independently in parallel and then compared. Disagreements were resolved through discussion and further consultation with the methodologist if needed. Panelists were divided into pairs for data extraction, with one performing data extraction and the other independently reviewing the initial data extraction. The methodologists assisted in building evidence tables and added data necessary for conducting any meta-analyses. Data from new studies identified in updated searches of published systematic reviews and data from de novo reviews were extracted into evidence tables (see e-Tables 4, 5 in the supporting data [see the "Availability of Companion Documents" field]).

### Quality Assessment

The methodologists assessed the quality of the guidelines using AGREE II and DART. Randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias tool. One researcher developed a quality assessment tool for intervention studies, including RCTs and observational studies, that was used to assess the quality of any observational studies included in the evidence reviews. As the methodologists were assessing the

quality of the studies, they also considered how exacerbations were counted and whether the outcomes were treated as primary or secondary outcomes.

### Meta-analyses and Evidence Profiles

Upon completion of the evidence tables and quality assessment, Review Manager version 5.1 software (The Cochrane Collaboration) was used to create meta-analyses on topics where data were homogeneous and poolable based on the measured outcomes. Studies with a shorter follow-up period (i.e., 3 to 4 months) were examined separately from those with a longer follow-up period (i.e.,  $\geq 6$  months). When possible, meta-analyses included studies from published systematic reviews as well as new studies identified through updated searches. Meta-analyses were also used for data compiled from de novo reviews. Heterogeneity of the pooled results was assessed using a  $X^2$  test and Higgins  $I^2$ , and a forest plot was examined for consistency of the results. A Higgins  $I^2 \geq 50\%$  and  $P < .05$  indicated statistically significant heterogeneity. The random-effects model was chosen a priori as the appropriate model for pooling data. Results from the meta-analyses can be found in e-Tables 6 and 7 in the supporting data.

### Grading the Evidence Profiles

Evidence profiles were produced using GRADEpro software (GRADE Working Group). The GRADEpro software ranked the quality of the body of evidence using four categories: high, moderate, low, and very low (see the "Rating Scheme for the Strength of the Evidence" field). The quality of the evidence was then used to determine the strength of the supporting evidence that informed a recommendation (see the "Description of Methods Used to Formulate the Recommendations" field for more information on grading recommendations). Additional information on grading the body of evidence can be found in "Methodologies for the Development of American College of Chest Physicians (CHEST) Guidelines and Expert Panel Reports" (see the "Availability of Companion Documents" field). Evidence profiles can be found in e-Tables 8 to 10 in the supporting data.

## Methods Used to Formulate the Recommendations

### Expert Consensus

## Description of Methods Used to Formulate the Recommendations

Evidence tables, meta-analyses, evidence profiles, and all the studies included in the evidence review informed the recommendations and their associated grades. Recommendations were graded using the American College of Chest Physicians (CHEST) grading system (see the "Rating Scheme for the Strength of the Recommendations" field). Values and preferences statements are considered part of a recommendation, and they appear with the recommendation in the main text of the guideline as well as in the summary of recommendations and executive summary. Panelists who were approved with management refrained from writing treatment-related recommendations and were assigned to drafting supporting text. Only one panelist in the population, intervention, comparator, outcome (PICO) 1 nonpharmacologic therapies group was prohibited from writing treatment-related recommendations. Two panelists in the PICO 2 inhaled therapies group were permitted to write recommendations, and they worked with the other panelists in the group to draft supporting text. Three panelists in the PICO 3 oral therapies group were permitted to write recommendations, and they worked with the other panelists to draft the supporting text. Recommendations were not made in instances where the panelists believed the data insufficient or inconclusive to warrant a recommendation. In instances where there was insufficient evidence but a recommendation was still warranted, a weak suggestion was developed, and consensus based (CB) replaced the grade. Completed recommendations/suggestions and supporting text were reviewed by each PICO group and revised before shared with the entire panel.

Recommendations/suggestions and supporting text were sent to the panelists along with a survey of the recommendations/suggestions asking panelists to identify any recommendations deemed controversial based on wording, grade, or both. Any recommendations identified as controversial in the survey as well as any CB suggestions were presented and discussed during a live webinar. Panelists were then sent an additional survey with the revised statements resulting from the discussions and asked to vote on the recommendations/suggestions. The conflict of interest grids were sent with the voting survey, and panelists approved with management were on the honor system to refrain from voting on any treatment-related recommendations. Based on CHEST policy, 75% participation and 80% consensus were required for recommendations/suggestions to pass. Any recommendations/suggestions that did not pass were revised based on feedback included in the voting survey, and a new survey was sent with the incorporated changes.

## Rating Scheme for the Strength of the Recommendations

Grade of Recommendation	Balance of Benefit vs. Risk and Burdens	Methodological Strength of Supporting Evidence	Implications
Graded evidence-based guideline recommendations			
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient's or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patient's or societal values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Nongraded consensus-based suggestions			
Consensus-based (CB)	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on confidence in the estimate of effect and may change the estimate.

## Cost Analysis

- In 2009, chronic obstructive pulmonary disease (COPD) caused 8 million office visits, 1.5 million emergency department (ED) visits, 715,000 hospitalizations, and 133,965 deaths in the United States. In 2010, U.S. costs for COPD were projected to be approximately \$49.9 billion, including \$29.5 billion in direct health-care expenditures, \$8.0 billion in indirect morbidity costs, and \$12.4 billion in indirect mortality costs. Exacerbations account for most of the morbidity, mortality, and costs associated with COPD. The economic burden

associated with moderate and severe exacerbations in Canada has been estimated to be in the range of \$646 million to \$736 million per annum. This value may be an underestimate given that the prevalence of moderate exacerbations is not well documented, COPD is underdiagnosed, and the rate of hospitalization due to COPD is increasing.

- Exacerbations are to COPD what myocardial infarctions are to coronary artery disease: They are acute, trajectory-changing, and often deadly manifestations of a chronic disease. Exacerbations cause frequent hospital admissions, relapses, and readmissions; contribute to death during hospitalization or shortly thereafter; reduce quality of life dramatically; consume financial resources; and hasten a progressive decline in pulmonary function, a cardinal feature of COPD. Hospitalization due to exacerbations accounts for >50% of the cost of managing COPD in North America and Europe.
- A cost-effectiveness analysis was performed on a randomized clinical trial comparing the effectiveness of a high-intensity smoking cessation intervention vs a medium-intensity strategy.<sup>72</sup> After 1 year, the high intensity strategy (individual counseling sessions, telephone contacts, small-group counseling sessions, and pharmacologic support) was associated with a higher continuous abstinence rate (salivary cotinine-validated abstinence at 6 and 12 months, 19% vs 9%, respectively; relative risk, 2.22; 95% confidence interval [CI], 1.06-4.65;  $P = 5 .03$ ). Additionally, the high-intensity strategy was associated with lower cost (€581 vs €595), a lower average number of exacerbations (0.38 vs 0.60), and a reduced number of hospital days (0.39 vs 1.00) per patient.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

### Review Process

After the acute exacerbations of chronic obstructive pulmonary disease (AECOPD) Guideline Executive Committee provided final approval, the manuscript was sent to the Executive of the Canadian Respiratory Guidelines Committee (CRGC), Canadian Thoracic Society (CTS) Executive, and CHEST reviewers representing the Guidelines Oversight Committee (GOC), Board of Regents, and NetWorks. The CHEST NetWorks of interested members in the areas of airways disorders and clinical pulmonary medicine reviewed the manuscript content. All reviewed both content and methods for consistency, accuracy, and completeness. The *CHEST* Journal peer-review process was integrated with these reviews. All ideas for modification were marked as mandatory or suggested by the GOC, responded to or justified by the authors, and tracked through multiple rounds of review.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Prevention of acute exacerbations of chronic obstructive pulmonary disease (COPD)

### Potential Harms

- Risks associated with short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, insomnia, infection, osteoporosis, and adrenal suppression
- Analyses of a broader pool of patients with chronic obstructive pulmonary disease (COPD) and in elderly patients in general (only a

minority of whom had COPD) found a significant increase in the occurrence of local adverse reactions with vaccines, but the effects were generally mild and transient.

- Although inhaled corticosteroid therapy may benefit some patients with COPD, it also increases the risk of systemic adverse effects, including pneumonia.
- The main adverse events reported in studies involving carbocysteine were mild gastrointestinal (GI) symptoms
- Clinicians prescribing macrolides need to consider in their individual patients the potential for prolongation of the QT interval and hearing loss as well as bacterial resistance.
- Physicians should use the lowest effective dose in prescribing theophylline in order to avoid adverse effects. Theophylline use requires vigilance on the part of the physician in order to avoid serious drug interactions, which lead to changes in serum theophylline levels. Patients should be advised that changes in tobacco use habits will affect serum theophylline levels and that they should inform their physicians if they stop smoking while taking theophylline.
- In patients with COPD and chronic bronchitis, N-acetylcysteine is well tolerated except for in rare patients with adverse GI effects.

## Qualifying Statements

### Qualifying Statements

American College of Chest Physicians and Canadian Thoracic Society guidelines and other clinical statements are intended for general information only and do not replace professional medical care and physician advice, which always should be sought for any medical condition. The complete disclaimer for this guideline can be accessed at <http://www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-Statements/CHEST-Guidelines> .

## Implementation of the Guideline

### Description of Implementation Strategy

#### Dissemination, Implementation, and Knowledge Translation

After publication, the guidelines were promoted by both American College of Chest Physicians (CHEST) and Canadian Thoracic Society (CTS) to a wide audience of physicians, other health-care providers, and the public through multiple avenues. Joint press releases were made to both the lay and the medical media, with major outreach efforts to all relevant print, broadcast, and Internet media. Panelists located in various large media markets were identified as potential spokespersons for interviews. In addition to the guidelines, a companion article was prepared to help with implementation.

American College of Chest Physicians: Social media promotion was facilitated over Twitter, Facebook, CHEST e-Communities, internal and external blogs, and other communication routes. Blast communications were sent to CHEST members with links to the publication and postings on the CHEST Web site.

In addition to publication in *CHEST*, other derivative products were prepared to help with implementation, including slide sets, algorithms, and other clinical tools. These derivative products were posted on the CHEST Web site and made available in CHEST Guidelines expected to launch at a later date. CHEST Guidelines will be the repository for the most current recommendations/suggestions from all CHEST guidelines, consensus statements, and hybrid documents. This online repository will also house a collection of related resources.

Canadian Thoracic Society: The knowledge translation plan was developed by (1) identifying key messages from the guideline recommendations, (2) determining the target audiences for each message, (3) seeking out the most credible messenger and engaging his or her interest in becoming involved in the communication, and (4) launching a knowledge translation strategy grounded in the best available research evidence. The CTS has a framework for guideline dissemination and implementation, with concurrent evaluation led by the Canadian Respiratory Guidelines Committee (CRGC) based on the Knowledge-to-Action Framework. Traditional knowledge diffusion avenues, such as presentations at scientific meetings and publication in peer-reviewed journals, will be used. The guideline was promoted through the CRGC Web site ([www.respiratoryguidelines.ca](http://www.respiratoryguidelines.ca) ). Targeted promotional communications were sent to provincial lung associations across Canada and distributed through CTS e-bulletins to individuals and organizations with an interest in this topic area.

CTS used other modes of communication such as briefing notes, Web sites, creative media, and emerging online technologies (e.g., podcasting, accredited webinars). To disseminate more broadly to the general public, traditional media and social media were engaged. Point-of-care tools for implementation of guideline recommendations were developed, including a trifold pocket brochure (Slim Jim) and electronic versions of the guideline for the smart phone and tablet. A slide kit for teaching and self-directed learning was posted for viewing and downloading on the CRGC Web site.

## Implementation Tools

Quick Reference Guides/Physician Guides

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Living with Illness

Staying Healthy

### IOM Domain

Effectiveness

## Identifying Information and Availability

### Bibliographic Source(s)

Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, Curren K, Balter MS, Bhutani M, Camp PG, Celli BR, Dechman G, Dransfield MT, Fiel SB, Foreman MG, Hanania NA, Ireland BK, Marchetti N, Marciniuk DD, Mularski RA, Ornelas J, Road JD, Stickland MK. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015 Apr;147(4):894-942. [285 references] [PubMed](#)

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2015 Apr

### Guideline Developer(s)

American College of Chest Physicians - Medical Specialty Society

## Source(s) of Funding

### Funding/Support

The American College of Chest Physicians and the Canadian Thoracic Society supported the development this article and the innovations addressed within.

## Guideline Committee

Expert Panel

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

The authors have reported to *CHEST* the following conflicts of interest: Dr Bourbeau received government grants for conducting the longitudinal population-based Canadian Cohort Obstructive Lung Disease (CanCOLD) study from the Canadian Institute of Health Research (CIHR) Rx&D collaborative program (AstraZeneca, Boehringer Ingelheim GmbH, GlaxoSmithKline plc, Merck Sharp & Dohme Corp, Nycomed, Novartis AG), Canadian Respiratory Research Network, Respiratory Health Network of the Fonds de recherche du Québec-Santé, and Research Institute of the McGill University Health Centre. Ms Diekemper is a co-developer of the DART (Document and Appraisal Review Tool), which was used in the AECOPD Guideline to assess the quality of the systematic reviews that informed some of the recommendations. Dr Hernandez reports that his institution has received pharmaceutical company grant monies for research studies on which he has been an investigator, including CSL Behring, Boehringer Ingelheim GmbH, and Grifols International SA. His institution also has received grant monies for research studies for which he has been an investigator, including CIHR and Lung Association of Nova Scotia. He has participated in speaking activities, industry advisory committees, and other activities related to industry sources with the following pharmaceutical companies: Actelion Pharmaceuticals US, Inc; Almirall, SA; AstraZeneca; Boehringer Ingelheim GmbH; GlaxoSmithKline plc; Grifols; Intermune; Merck Sharp & Dohme Corp; and Novartis AG. Dr Balter has served over the past 3 years on advisory boards for and has presented at continuing education meetings for Almirall, SA; AstraZeneca; Boehringer Ingelheim GmbH; GlaxoSmithKline plc; Merck Frosst Canada Inc; Novartis AG; and Takeda Pharmaceutical Company Limited. Dr Bhutani receives university grant money, pharmaceutical grant money, grant money from government organizations in Canada and participates in speakers bureaus and speaks publicly on the topic of acute exacerbations of COPD. Dr Camp has received operating grant funding from CIHR, Canadian Lung Association, and Physiotherapy Foundation of Canada. She has received research infrastructure funding from the Canadian Foundation of Innovation and the British Columbia Lung Association and a scholar award from the Michael Smith Foundation of Health Research. She has received honoraria for speaking engagements from the Canadian Lung Association and the University of British Columbia Respiratory Division. Dr Celli's division has received grants from AstraZeneca to complete research studies. He has served on an advisory board or as a consultant to GlaxoSmithKline plc; Boehringer Ingelheim GmbH; Almirall, SA; AstraZeneca; Takeda Pharmaceutical Company Limited; and Novartis AG. Neither he nor any member of his family has shares or interest in any company. Dr Celli has not received or had any relationship with tobacco money. Dr Dechman speaks to health professionals about the management of COPD, including acute exacerbations of COPD, but does not gain financially from doing so. Dr Dransfield has served as a consultant for GlaxoSmithKline plc; Boehringer Ingelheim GmbH; and Ikaria, Inc. His institution has received research grant support from the American Heart Association; National Heart, Lung, and Blood Institute; GlaxoSmithKline plc; and Forest Laboratories, Inc, and has received contracted support for enrollment in clinical trials from Aeris; Boehringer Ingelheim GmbH; Boston Scientific Corporation; Janssen Biotech, Inc (formerly Centocor Biotech, Inc); GlaxoSmithKline plc; Forest Laboratories, Inc; Otsuka America Pharmaceutical, Inc; Pearl Therapeutics Inc; Pfizer, Inc; PneumRx, Inc; and Pulmonx. Dr Fiel has received grant support from the Cystic Fibrosis Foundation and grants for clinical trials from Vertex Pharmaceuticals Incorporated, Gilead, Novartis AG, and PTC Therapeutics. Dr Foreman is PI for the Forest ASCENT COPD study (LAS-MD-45). Dr Hanania serves as a consultant to Boehringer

Ingelheim GmbH; Sunovion Pharmaceuticals Inc; Novartis AG; Mylan Inc; Pearl Therapeutics Inc; and Pfizer, Inc. Her institution receives grant support on her behalf from GlaxoSmithKline plc; Boehringer Ingelheim GmbH; Pfizer, Inc; Pearl Therapeutics Inc; and Sunovion Pharmaceuticals Inc. Dr Marchetti has served as principal investigator for a pharmaceutical-funded clinical trial with GlaxoSmithKline plc. Dr Marciniuk has provided consultation for Health Canada, the Public Health Agency of Canada, and the Saskatoon Health Region. He has received research funding (all held and managed by the University of Saskatchewan) from AstraZeneca; Boehringer Ingelheim GmbH; CIHR; Forest Laboratories Inc; the Lung Association of Saskatchewan; Novartis AG; Pfizer, Inc; Saskatchewan Health Research Foundation; and Schering-Plough Corporation. He holds fiduciary positions with the American College of Chest Physicians, the Chest Foundation, and the Lung Health Institute of Canada. Drs Criner, Ouellette, Goodridge, Ireland, Mularski, Road, and Stickland; Ms Curren; and Mr Ornelas have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

## Guideline Endorser(s)

Canadian Respiratory Health Professionals - Professional Association

International Primary Care Respiratory Group - Professional Association

U.S. COPD Coalition - Nonprofit Organization

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Electronic copies: Available from the [CHEST Journal Web site](#) .

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

## Availability of Companion Documents

The following are available:

- Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. Supporting data. 2015 Apr. 101 p. Electronic copies: Available from the [CHEST Journal Web site](#) .
- Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. Executive summary. Chest. 2015 Apr;147(4):883-893. Electronic copies: Available from the [CHEST Journal Web site](#) .
- Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. Podcast. 2015 Apr. Available from the [CHEST Journal Web site](#) .
- Methodologies for the development of CHEST guidelines and expert panel reports. Chest. 2014 Jul;146(1):182-192. Electronic copies: Available from the [CHEST Journal Web site](#) .

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on June 3, 2015.

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